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Datasheet for the decision of 15 December 2011

Case Number: T 1607/07 - 3.3.02

Application Number: 01932484.7

Publication Number: 1289505

IPC: A61K 9/72

Language of the proceedings: EN

Title of invention:
Process of producing a stable pharmaceutical composition containing micronized formoterol

Applicant:
AstraZeneca AB

Opponent:
INNOVATA BIOMED LIMITED

Headword:
Formoterol composition/ASTRAZENECA

Relevant legal provisions:
EPC Art. 56

Relevant legal provisions (EPC 1973):
-

Keyword:
"Inventive step (no): Improvement not proved to be related to distinguishing feature; feature added without effect"

Decisions cited:
-

Catchword:
-

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Case Number: T 1607/07 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 15 December 2011

Appellant: (Opponent)
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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted 13 July 2007 concerning maintenance of European patent No. 1289505 in amended form.

Composition of the Board:

Chairman: U. Oswald
Members: H. Kellner
L. Bühler

Summary of Facts and Submissions

I. European patent No. 1 289 505, based on international application PCT/SE2001/001117 and published as WO 2001/089491, was granted with 12 claims.

Independent process-claim 1 and product-claim 6 as granted read as follows:

"1. A process for preparing a pharmaceutical composition comprising, in admixture, an active ingredient which is micronised formoterol or an enantiomer thereof, optionally in the form of a salt or solvate or a solvate of a salt, and a micronised carrier/diluent, which process comprises
Step 1: preparing a mixture of micronised active ingredient and carrier/diluent,
Step 3: either subjecting the mixture to agglomeration and spheronisation, or adding coarse carrier/diluent,

wherein process step 2 is added between steps 1 and 3 and consists in the addition of further pre-micronised carrier/diluent which is mixed in at low energy.

6. A pharmaceutical composition comprising, in admixture, an active ingredient which is micronised formoterol optionally in the form of a salt or solvate or a solvate of a salt, and a micronised pharmaceutically acceptable carrier/diluent, characterised in that the composition is obtainable by the process according to claim 1 and the composition has a high storage stability such that decomposition of formoterol in the formulation will be less than 10% when stored in open dishes at 40°C and 75% relative

humidity for 6 months when the content of formoterol is less than 1% (w/w) or less than 2.5% when stored in a dry powder inhaler under the same conditions."

II. Opposition was filed against the granted patent under Articles 100(a), (b) and (c) EPC. Under Article 100(a) objections were raised regarding inventive step only.

The documents cited during the proceedings before the opposition division and the board of appeal included the following:

(1) WO 98/31351 A1

(3) WO 95/05805 A1

(16) US 5 478 578.

III. The opposition division held with respect to the auxiliary request before it that the requirements of Article 123(2) EPC were fulfilled, because compositions comprising more than 0.6% formoterol were not sufficiently disclosed; for those comprising less than 0.6% formoterol, however, a storage profile was provided and a limitation to these did not extend the subject-matter of the request beyond the content of the application as originally filed.

As far as Article 83 EPC was concerned, in view of the examples in the description the patent contained sufficient information to enable the skilled person to produce without undue burden the composition referred to in claims 6 to 12 of the auxiliary request and the opponent had provided no evidence to the contrary.

There was also enough information in the patent to carry out the claimed process (claims 1 to 5).

Closest prior art was document (1). The teaching of the patent in suit was new and inventive over this state of the art because of the additional activity in the process (addition of further carrier/diluent in step 2) and the improved storage stability with respect to document (1).

IV. The appellant (opponent) and the patent proprietor each lodged an appeal against that decision. Grounds of appeal were filed by the opponent only.

V. The patent proprietor, as an answer to the statement of grounds of appeal of the appellant (opponent), defined its main request as the set of claims as maintained by the opposition division and filed its first auxiliary request with letter of 6 June 2008; two further sets of claims were filed with letter of 2 December 2011 as second and third auxiliary requests; in both these sets of claims, claims 6 to 10 relating to compositions and the further use-claims 11 and 12 were deleted.

VI. On 15 December 2011, oral proceedings took place before the board.

The patent proprietor confirmed that it had not filed grounds of appeal and that it had respondent status in the appeal proceedings.

The appellant did not comment on the process-claim 1 of the requests except to comment on the extent of an effect that a conditioning step could have on the

chemical stability of the composition obtained by the claimed process.

During the oral proceedings, the respondent filed a fourth auxiliary request which was not admitted into the proceedings.

The wording of claim 1 as granted and the wording of claim 1 of the main request and that of the second auxiliary request are identical.

In claim 1 of the first auxiliary request the wording "mixed in at low energy" was replaced by "mixed in at a pressure below 2 bar".

In claim 1 of the third auxiliary request, with respect to claim 1 of the main request, the alternative under step 3 relating to "adding coarse carrier/diluent" was deleted.

In claim 1 of the fourth auxiliary request, with respect to claim 1 of the main request, at the end of the claim the wording "and wherein the mixture is conditioned between steps 1 and 2 and the further pre-micronised carrier/diluent is conditioned at step 2" was added.

VII. At oral proceedings, the appellant mainly relied on its written case; its submissions can be summarised as follows:

The experiments on file did not qualify as proof that the process according to the patent would result in improved storage stability. For instance, it was not

demonstrated that the improved stability of the composition of example 2 of the patent resulted from the additional step as provided by claim 1 of this patent; there, the conditioning step performed in example 2 was not included. Consequently, the problem to be solved was only the provision of an alternative with respect to the state of the art and the introduction of the additional and superfluous step of adding further pre-micronised carrier/diluent at low energy, as defined in claim 1, could not give rise to an inventive step.

In addition, the appellant submitted during the oral proceedings that a conditioning step as mentioned in example 2 of the patent in suit and directed to restoring the crystal structure in a controlled way was not shown to have no effect on the product obtained, such as influencing its chemical stability.

VIII. The respondent's arguments may be summarised as follows:

The objection of missing inventive step was based neither on the demonstration of the characterising feature of the invention as anticipated in the state of the art nor on experimental evidence provided by the appellant. The examples of the patent in suit together with the experimental data submitted during the grant proceedings represented sufficient evidence to demonstrate the improvement provided by the teaching of the patent in suit, and in particular by additional step 2. There was no evidence in the state of the art to make the additional provision of pre-micronised carrier/diluent obvious.

The process-steps of example 2 of the patent in suit differing from its example 1 or its claim 1 respectively were:

- a longer mixing time of formoterol fumarate dihydrate and lactose monohydrate,
- the conditioning of the further added lactose monohydrate (according to step 2) and
- the particular definition of relative humidity to be kept during the spheronising step in example 1 only.

None of these differences could affect the chemical stability of the product. In particular, the result of applying the step of conditioning to the lactose monohydrate to be further added was restricted to maintaining the fraction of respirable particle as could be seen from lines 24 to 31 on page 10 of document (3).

IX. The appellant (opponent) requested that the decision under appeal be set aside and that the European patent No. 1289505 be revoked.

X. The respondent (patent proprietor) requested that the appeal be dismissed or, alternatively, that the decision under appeal be set aside and that the patent be maintained on the basis of the set of claims filed as first auxiliary request with letter of 6 June 2008, or on the basis of one of the sets of claims filed as second and third auxiliary request with letter of 2 December 2011, or on the basis of the set of claims submitted as fourth auxiliary request during oral proceedings.

Reasons for the Decision

1. The appeal of the opponent is admissible.

2. No written statement setting out the grounds of appeal was filed by the patent proprietor within the time limit under Article 108, third sentence, EPC in conjunction with Rule 126(2) EPC. Therefore, the patent proprietor's appeal was rejected as inadmissible (Rule 101(1) EPC).

   Consequently, and as acknowledged, the patent proprietor had the status as respondent to the opponent's appeal.

3. *Admissibility of the fourth auxiliary request*

   Patentability of independent process-claim 1 as granted was already disputed in the notice for opposition and in the statement of grounds of appeal, in particular on the basis of the arguments set out under point VII of this decision *inter alia* referring to the conditioning of pre-micronised lactose in step 2. These arguments, as the appellant already submitted in writing, led to lack of inventive step.

   Consequently, the respondent could have already taken account of these submissions and filed an auxiliary request much earlier during the proceedings.

   In addition, the introduction of the process step of conditioning would have given rise to a number of issues which could not reasonably have been expected to be dealt with at this late stage of the proceedings.

Therefore, the fourth auxiliary request was not admitted into the proceedings.

4. *Claim 1 of the main request; Article 56 EPC (inventive step)*

4.1 With regard to its claim 1, the patent in suit relates to a process for preparing a pharmaceutical composition comprising, in admixture, an active ingredient which is micronised formoterol ..., and a micronised carrier/diluent,
which process comprises

- Step 1: preparing a mixture of micronised active ingredient and carrier/diluent,
- Step 3: either subjecting the mixture to agglomeration and spheronisation, or adding coarse carrier/diluent
- wherein process step 2 is added between steps 1 and 3 and consists in the addition of further pre-micronised carrier/diluent
  - which is mixed in at low energy.

4.2 In the present case, for determining the document of closest prior art, there is no reason to deviate from the reasoning and conclusions of the opposition division. The closest prior art is document (1).

Document (1) relates to

a process for preparing a pharmaceutical composition comprising, in admixture, an active ingredient which is micronised formoterol ..., and a micronised carrier/diluent, (see claim 6 together with claim 1)

which process comprises

- Step 1: preparing a mixture of micronised active ingredient and carrier/diluent, (see claim 6, point (a))
- Step 3: either subjecting the mixture to agglomeration and spheronisation, ... (see claim 6, points (b) and (c)).

4.3 With respect to the comparative example 1 in the teaching of the patent in suit, according to its claim 1 the process step 2 is added between steps 1 and 3 and consists in the addition of further pre-micronised carrier/diluent.

In example 2 of the patent in suit, however, further pre-micronised carrier/diluent was added, including a conditioning treatment before the addition.

This step of conditioning represents an additional difference between the teaching of the patent in suit and example 1 and, consequently, it is either the addition of further micronised lactose monohydrate at this stage of the process or the conditioning that could have given rise to the improvement in stability indicated in example 2 of the patent in suit.

4.4 In these circumstances, there is no proof that the teaching of claim 1 of the patent in suit per se results in any improvement at all, and the problem to be solved has to be defined as the provision of another process of mixing formoterol hydrate and carrier/diluent in order to prepare a pharmaceutical formulation.

The inventive step of such provision cannot however be derived from a process step that does not relate to any purposive effect on the process or on the product obtained.

5. The further arguments of the respondent cannot succeed either.

5.1 The respondent had submitted that applying the step of conditioning to the lactose monohydrate to be further added was restricted to maintaining the fraction of respirable particles according to document (3).

5.1.1 From the text of example 2 in the patent in suit, however, it is not even clear that the conditioning step as applied to the micronised lactose monohydrate before addition to the composition really is a conditioning according to document (3).

Firstly, in example 2 itself, the treatment according to document (3) is characterised as "The crystal structure was restored in a controlled way according to US 5,874,063 or US 5,709,884." (document (3) is the international application forming the basis of US patent 5,709,884) and nothing in example 2 indicates that "conditioning" as applied to the further micronised lactose monohydrate would mean a "restoring of crystal structure" within the meaning of the teaching of the cited US patents.

Secondly, the fact that the word "conditioning" is cited somewhere in the description of the patent in suit in connection with document (3) does not provide for an exact definition (see column 2, line 46 to

column 3, line 3 of the patent in suit). It is only disclosed that "Conditioning **can** be carried out according to the procedures described in WO 95/05805 ..." (which is document (3) in the current proceedings; emphasis added by the board), which in principle leaves open the possibility that conditioning could be carried out in any way whatsoever.

5.1.2 Moreover, the fact that the effect of the additional conditioning step in step 2 of example 2, i.e. the further addition of pre-micronised lactose monohydrate, is disclosed in document (3) as being directed to maintaining the fraction of respirable particles does not limit its application to this effect. Document (3) does not exclude further effects the conditioning step could have.

5.2 Reference to the experimental data filed by the respondent during the grant proceedings (see letter of 22 October 2003, in particular page 2, last paragraph, lines 3/4 or 9 respectively) does not help, because these comparative data relate to experiments where a composition is simply described as produced "according to example 1 in document (1)" or another one, "according to the present invention", without any indication of the specific parameters of the experimental setup.

6. The arguments as set out in sections 4 and 5 of this decision also apply to claims 1 of the first to third auxiliary requests; their teaching also does not involve an inventive step (Article 56 EPC).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

N. Maslin U. Oswald